Adaptive Platform Trial Scientific Meeting

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CanTreatCOVID

Canadian Adaptive Platform Trial of Treatments for COVID in Community Settings

Evaluating Platform Designs for Clinical Trials in Patients with Mild Cognitive Impairment

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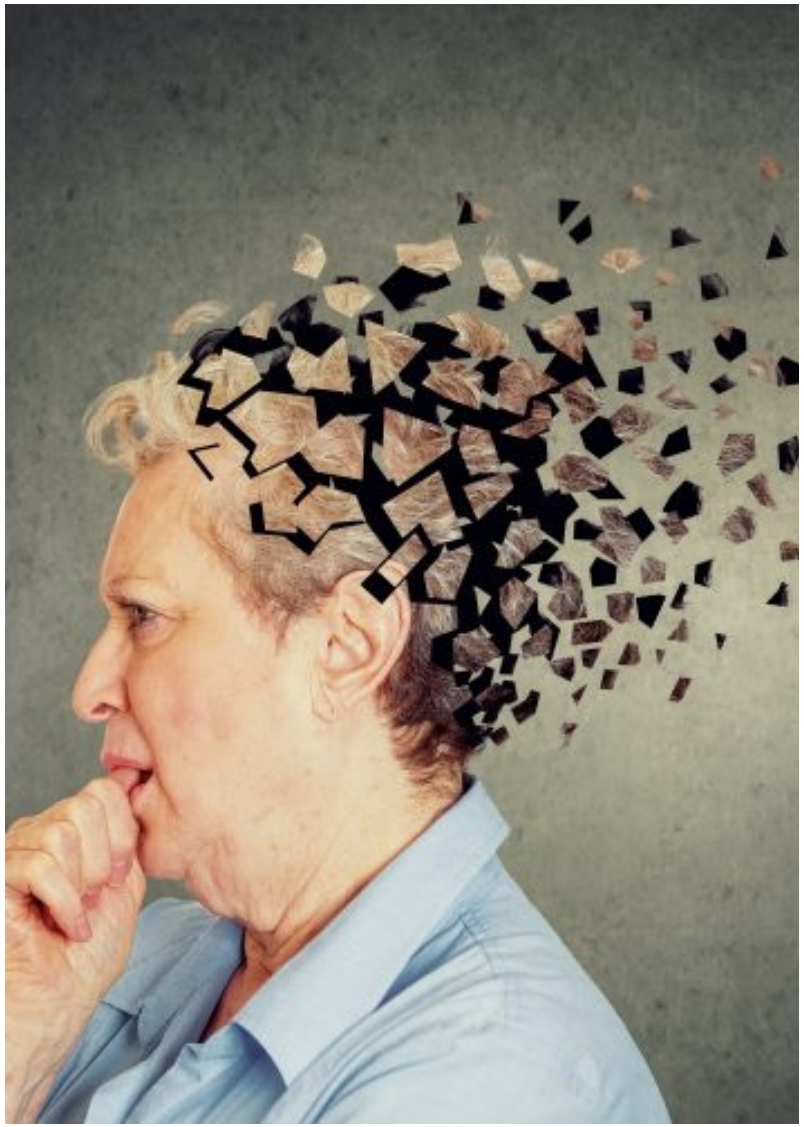
Mild Cognitive Impairment (MCI)

Definition: MCI is an early stage of memory loss or cognitive ability loss [1]

Epidemiology: prevalence increases with age; overall prevalence of MCI was 15.6% worldwide in community-dwelling adults aged 50 years and older [2]

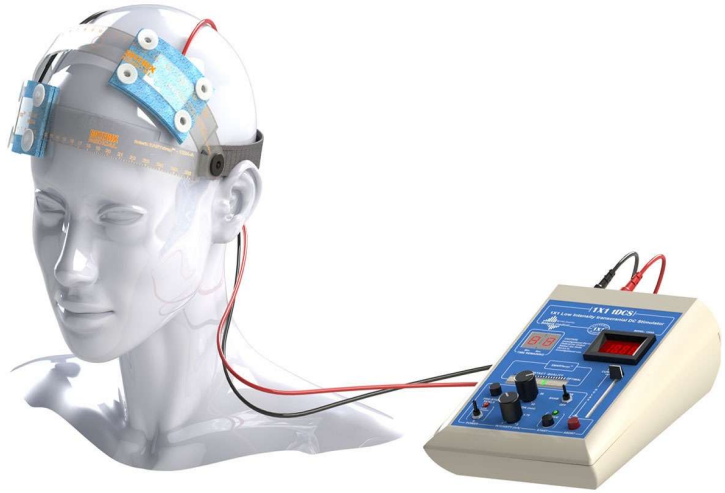
Impact: affects quality of life; risk of Alzheimer disease

Treatments: drug, cognitive training, physical activity, neurostimulation



Transcranial Direct Current Stimulation (tDCS)

- **tDCS**
  - A non-invasive brain stimulation technique
  - Use weak electrical currents to stimulate specific areas of the brain [3]
  - Potential to enhance cognitive function and treat neurological conditions [4]
- **tDCS trial:**
  - **PACt-MD** [4]: compare the efficacy of cognitive remediation (CR) + tDCS versus sham CR + sham tDCS in participants with a history of major depressive disorder MDD and/or MCI
  - Verify the potential of tDCS and its combination with other treatments in treating cognitive disorders



Theta burst stimulation (TBS)

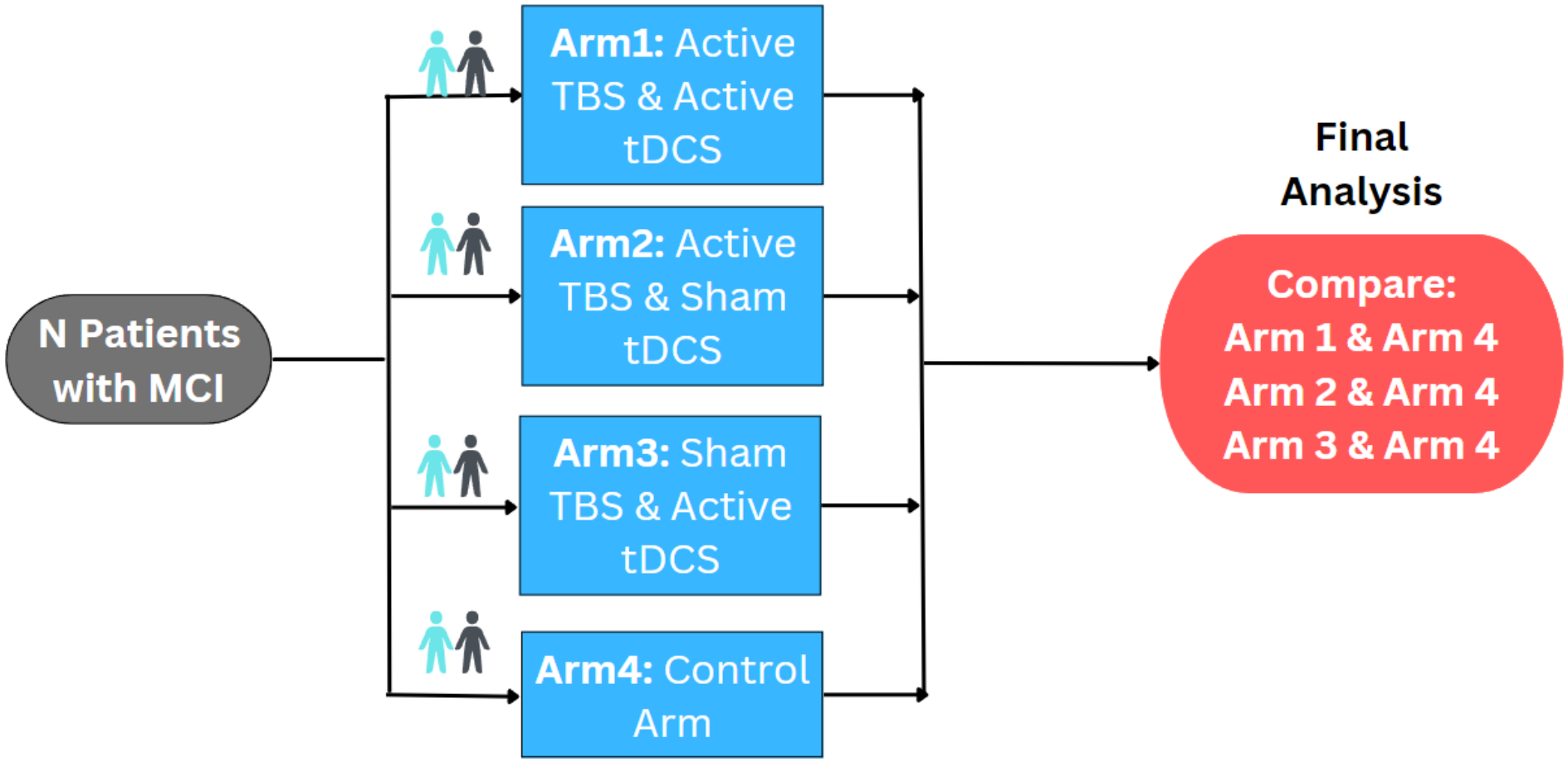
- **TBS**
  - A novel form of repetitive transcranial magnetic stimulation (rTMS) [5]
  - Offer a unique stimulation pattern mirroring the brain's natural theta rhythm.

- **TBS trial**
  - **FOUR-D Trial** [5]: to determine the effectiveness and tolerability of TBS compared to standard bilateral rTMS in treating older adults with Treatment-Resistant Depression (TRD).
  - TBS offers similar efficacy but with a much shorter treatment duration

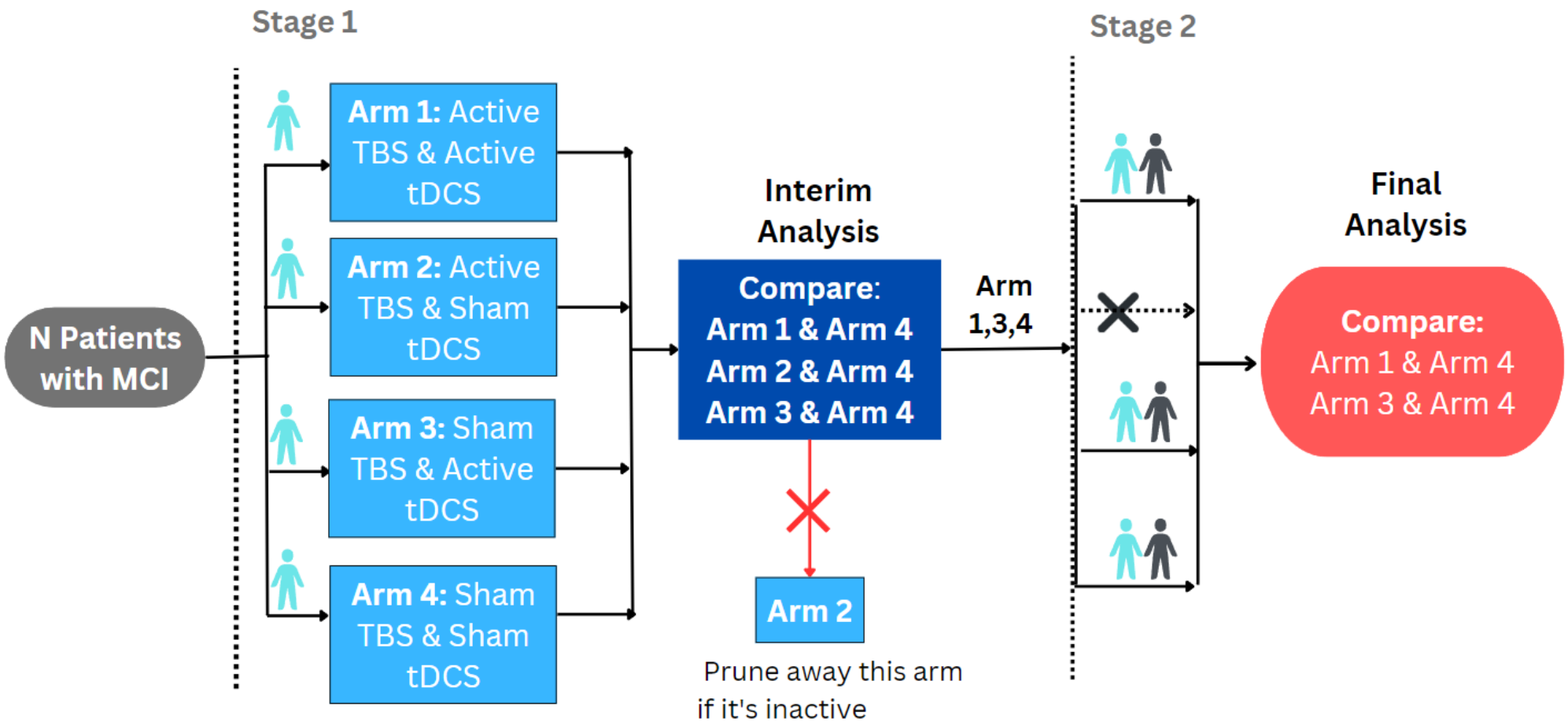
Planning for a combination tDCS + TBS trial

- **Background**: tDCS and TBS have different mechanisms of action on neurophysiology.
- **Primary objective**: To evaluate the efficacy of combined tDCS and TBS for the treatment of MCI.
- **Endpoint:** Montreal Cognitive Assessment (MoCA) (normal distribution)
- **Arms:**
  - Arm 1: Active TBS + Active tDCS
  - Arm 2: Active TBS + Sham tDCS
  - Arm 3: Sham TBS + Active tDCS
  - Arm 4: Sham TBS + Sham tDCS (Control)

1-Stage 4-Arm Platform Design for Evaluating TBS and tDCS



2-Stage 4-Arm Platform Design for Evaluating TBS and tDCS



Objective

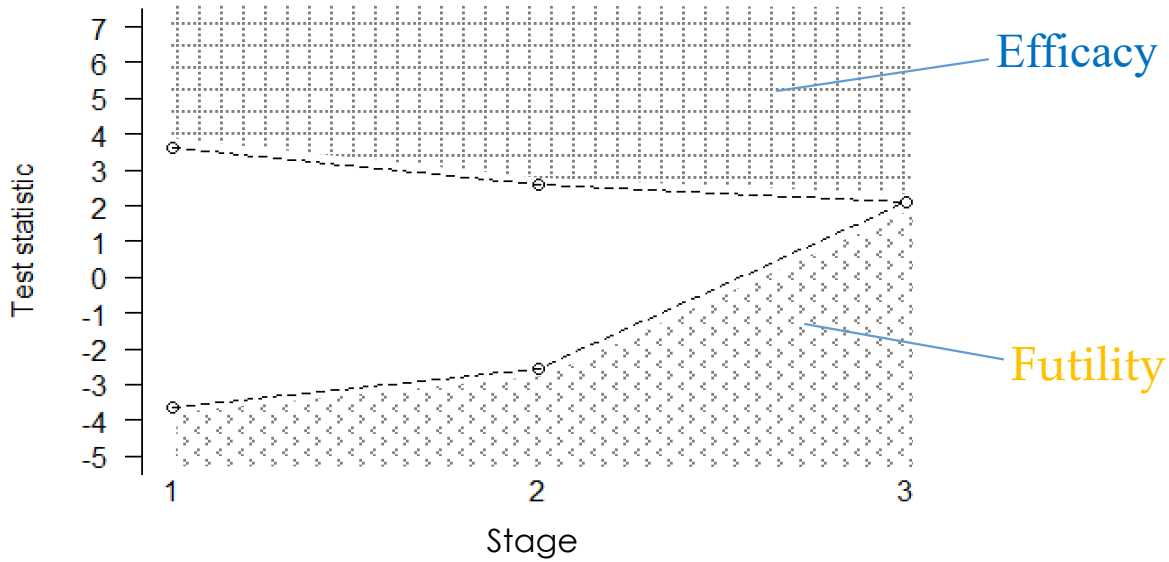
- To assess the feasibility of a muti-arm 2-stage platform design for tDCS + TBS trial
- To evaluate the power and operating characteristics of a 2-stage multi-arm platform design for a trial in patients with MCI

R Package: MAMS [6]

- Hypothesis: μ_k is the mean response of arm on treatment $k = 0, \ldots, K$

$$\boldsymbol{H_0}: \; H_{01}: \mu_1 = \mu_0, \ldots . , H_{0k}: \mu_k = \mu_0$$
$$\boldsymbol{H_1}: \; H_{11}: \mu_1 \neq \mu_0, \ldots . , H_{1k}: \mu_k \neq \mu_0$$

- Type 1 error control achieved using alpha spending approach:



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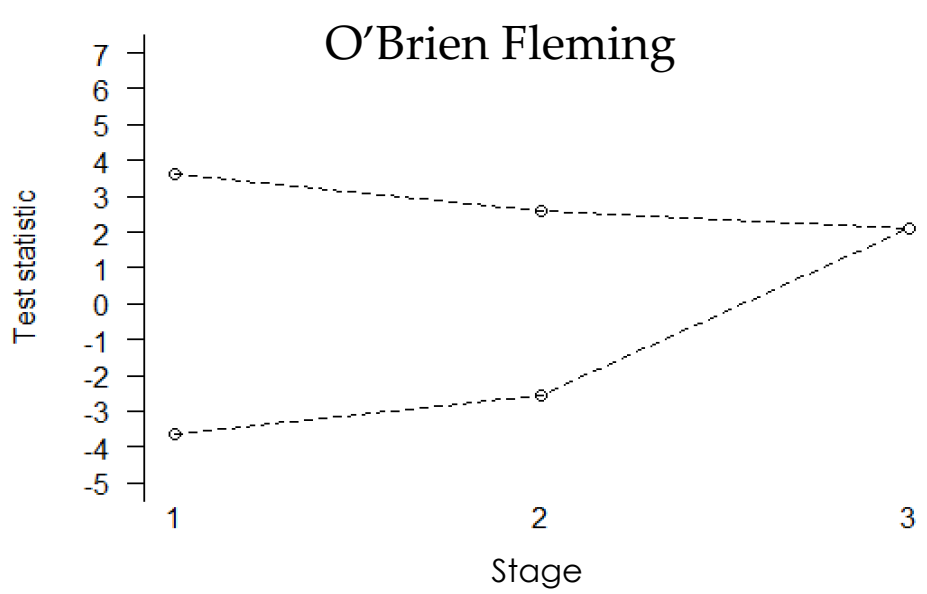
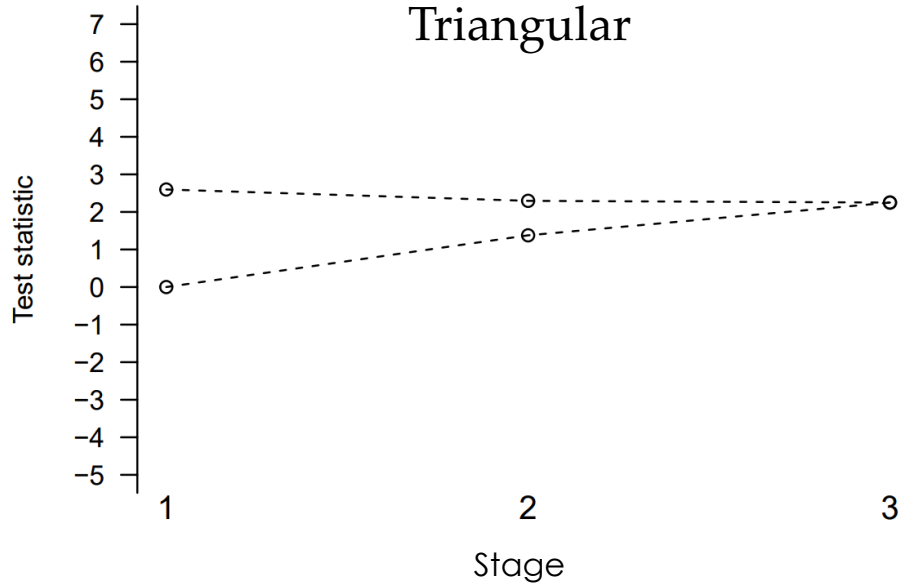




Input Parameters

Input Parameter	Definition	Values
Standardized effect size (Δ)	Standardized effect of each treatment arm vs. control arm	0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0
Alpha (α)	Two-sided familywise error rate	0.05
Power	The desired power (probability of rejecting the null hypothesis when it's false)	0.8, 0.9 (data not shown)
Boundary type	Alpha spending function	Triangular, Pocock, O'Brien Fleming
Timing of interim analysis	The accrual ratio of sample size at interim analysis	20%, 30%, 40% 50%, 60%, 70%, 80%
Stage	Number of stages	1, 2

Maximum, Expected sample size vs. Boundary type

Number of stage	Boundary type	Maximum sample size	Expected sample size
1	N/A	272	272
2	O'Brien-Fleming	280 (+ 3%)	225 (- 17%)
2	Pocock	304 (+ 11%)	195 (- 28%)
2	Triangular	312 (+ 15%)	196 (- 27%)

- One-stage trials demand a lower maximum sample size but tend to have a higher expected sample size
- Two-stage trial has a great potential for sample size reduction

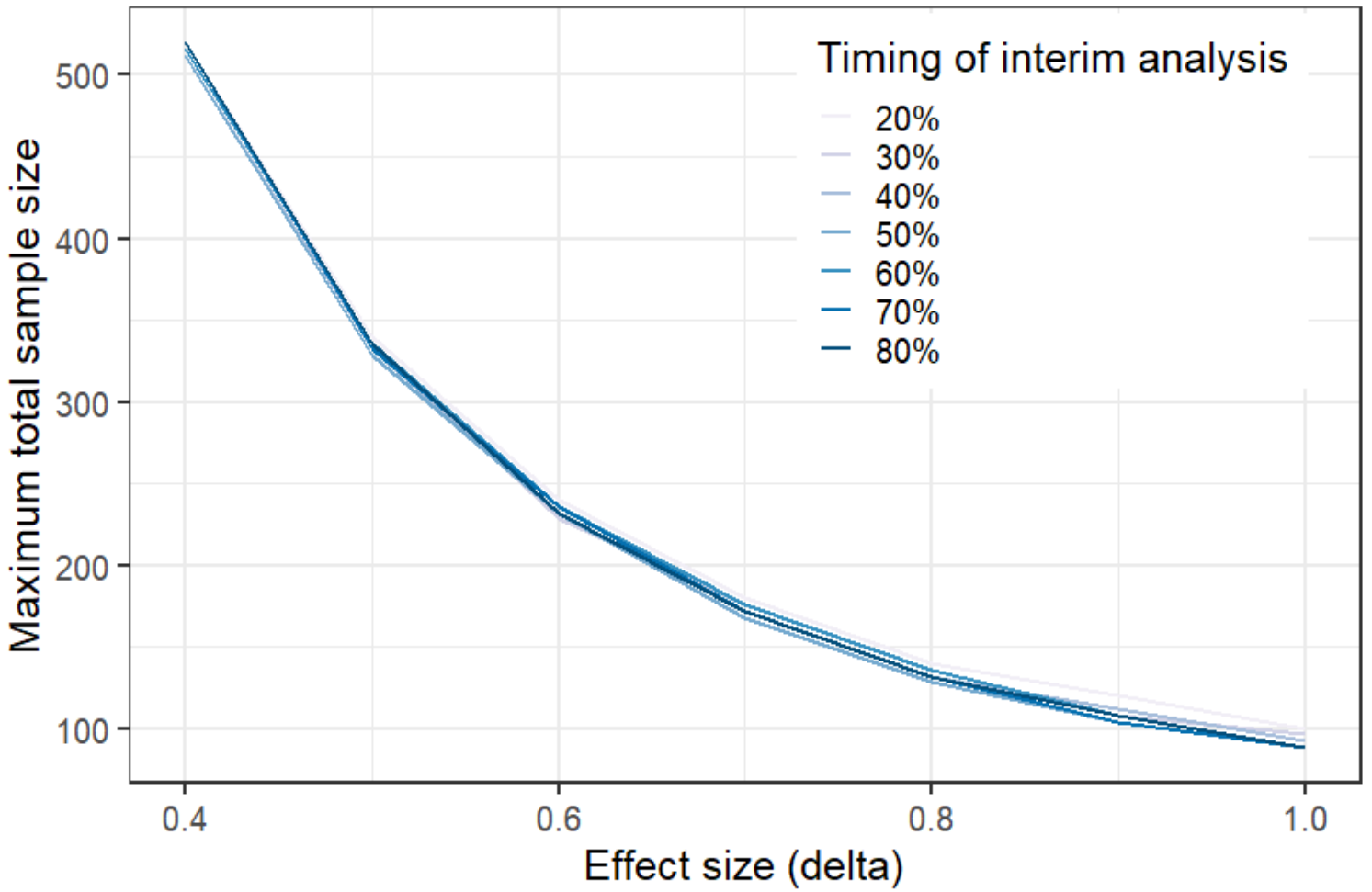
Maximum, Expected sample size vs. Boundary type

Number of stage	Boundary type	Maximum sample size	Expected sample size
1	N/A	272	272
2	O'Brien-Fleming	280 (+ 3%)	225 (- 17%)
2	Pocock	304 (+ 11%)	195 (- 28%)
2	Triangular	312 (+ 15%)	196 (- 27%)

- O'Brien-Fleming boundary type has the lowest maximum sample size, and Pocock has the lowest expected sample size
- Prefer O'Brien-Fleming boundary type

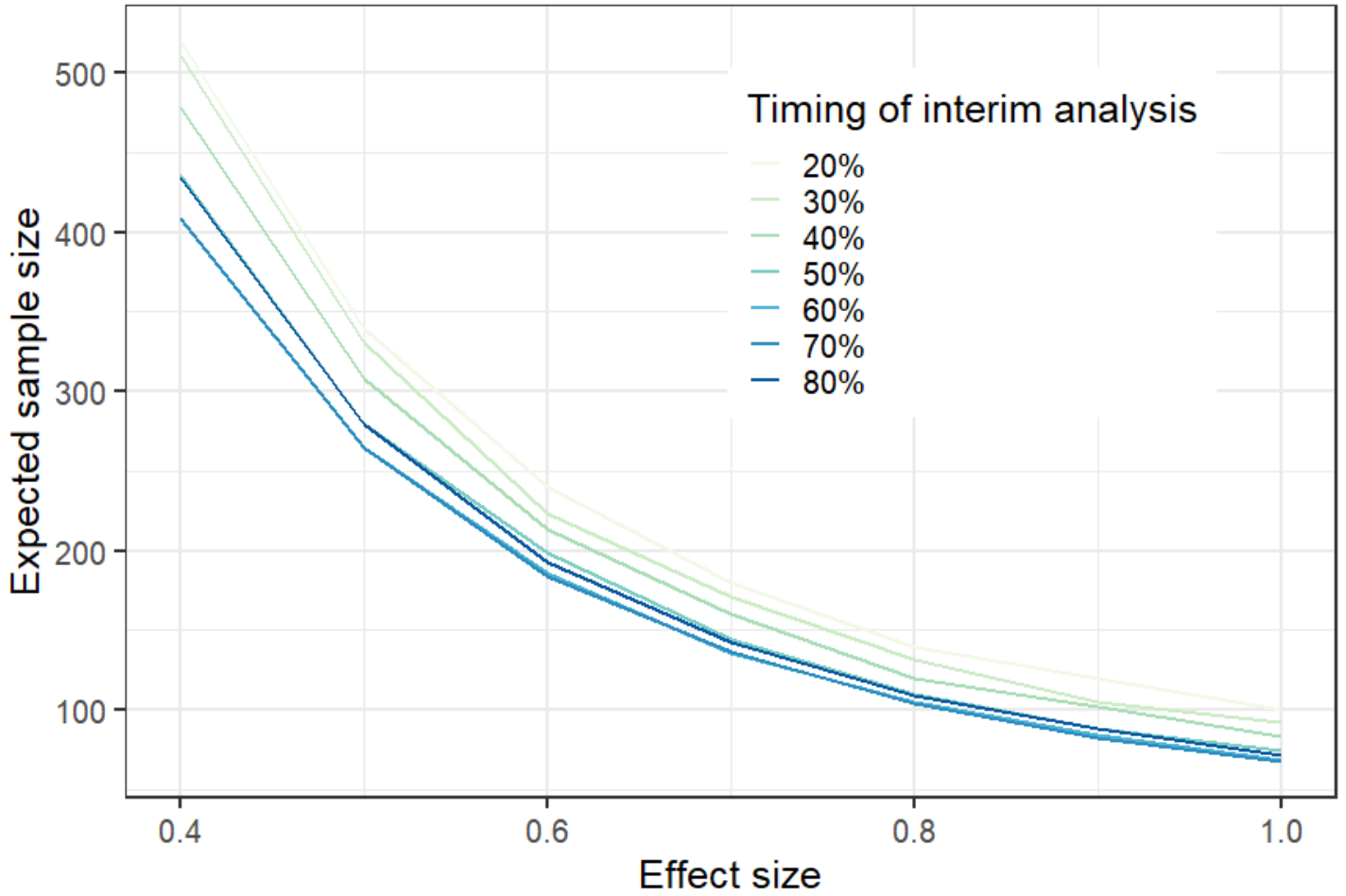
Maximum N by effect size and timing of interim analysis

- Increasing the initial sample size has a limited impact on the maximum sample size required.



All calculations done with power of 0.8 and alpha of 0.05 under O'Brien-Fleming boundary type.

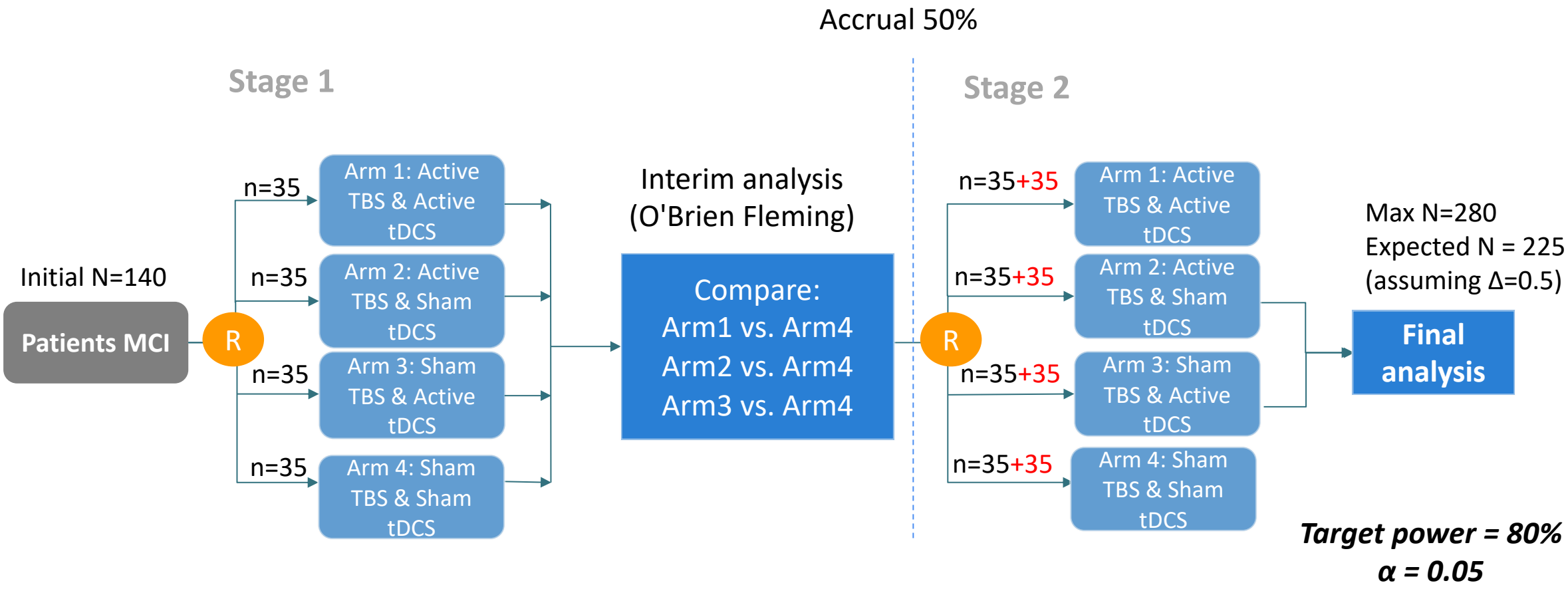
Expected N by different timing of interim analysis



All calculations done with power of 0.8 and alpha of 0.05 under O'Brien-Fleming boundary type.

- An increase in the timing of the interim analysis resulted in a gradual decline in the expected sample size.
- The expected sample size could even rise if the initial sample size is overly large.

2-Stage 4-Arm With Proposed Parameters



Advantages & Challenges of Platform Designs

- Advantages
  - **Reduced expected N**: early stopping for futility or efficacy reduces expected N.
  - **Type 1 error control**: alpha-spending approach controls trial-wide type 1 error.
  - **Shared control arm**: platform design reduces N vs. separate independent trials
- Challenges
  - **Increased complexity**: require more complex statistical planning and analysis.
  - **Increased maximum N**: potential for an increased sample size if interim analysis are inconclusive, potentially increasing cost of the study

Conclusions

- A multi-arm 2-stage platform design is potentially feasible and efficient for trials of neurostimulation interventions for treating people with mild cognitive impairment.
- Emphasized the trade-offs between boundary type selection, stage allocation for overall sample size requirements.
- Future work will assess Bayesian platform designs vs. frequentist approach

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Thanks

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